Doctoral Dissertation Defense Announcement

“Modulation of gut microbial metabolism and energy expenditure by xenobiotics and bacterial metabolites”

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Christopher Kristich, PhD
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Date: Thursday, May 9, 2024
Time: 11:00 AM (CST)

Defense Location: Kerrigan Auditorium

Zoom: https://mcw-edu.zoom.us/j/8534438321?pwd=MUQzY1V1bjNmN1IzWjZBZ1k4YjdLQT09
Meeting ID: 853 443 8321 Passcode: #8sT9QU0
**Graduate Studies:**

- Advanced Bacterial Physiology
- Bacterial Toxin-Mucosal Cell Interactions
- Classical Papers in Microbiology and Immunology
- Doctoral Dissertation
- Ethics and Integrity in Science
- Immunology Journal Club
- Integrated Microbiology and Immunology
- Microbiology and Immunology Seminar Course
- Reading and Research
- Research Ethics Discussion Series
Dissertation

“Modulation of gut bacterial metabolism and anaerobic energy expenditure by xenobiotics and bacterial metabolites”

Obesity is associated with serious comorbidities including heart disease, stroke, and cancer, and is one of the most challenging healthcare problems of our times. Thus, there is a critical need to identify and understand the mechanisms of obesity. Recently, the gut microbiome has been identified as a factor which can play a causative role in weight gain.

Studies in our lab demonstrated that the gut microbiota comprise a thermogenic biomass that contributes to resting metabolic rate. Acute reduction of bacterial biomass using cecectomy resulted in a ~10% decrease in total metabolic rate via suppression of anaerobic energy expenditure, which subsequently led to weight gain. Treatment with the antipsychotic, risperidone, suppresses anaerobic energy expenditure in a microbiome-dependent manner. In contrast, a specialized metabolite produced by Limosilactobacillus reuteri, reutericyclin (RTC), was capable of ameliorating risperidone-induced weight gain (RIWG) and restored energy balance in the presence of risperidone.

We performed comprehensive evaluations of energy balance in mice treated with risperidone, RTC, or in combination to identify a mechanism by which RTC affects energy balance to mitigate RIWG. We employed the Promethion metabolic phenotyping system as well as whole-animal calorimetry coupled with respirometry on C57BL/6J female mice to assess components of energy balance including resting metabolic rate. We observed that risperidone suppresses resting anaerobic metabolism and that RTC restores energy expenditure in the presence of risperidone. Treatment with either RTC or risperidone does not alter other components of aerobic energy expenditure. Because anaerobic energy expenditure has previously been demonstrated to be dependent on the biomass and composition of the gut microbiome, we performed sequencing on stool samples collected during the energy balance assessments described above. Risperidone and RTC treatments reciprocally modified the relative abundance of taxa known to participate in fermentation. For example, RTC administration resulted in increased relative abundance of Akkermansia muciniphila, which is consistently correlated with leanness in both humans and mice.

We also performed studies investigating the potential for RTC to promote lower body weight outside the context of risperidone treatment. Obese mice being fed a 60% high-fat diet exhibited reduced weight gain when treated with RTC. Additionally, mice treated with a relatively low dose of semaglutide exhibited enhanced weight loss when also treated with RTC. Treatment with RTC did not affect food consumption or digestive efficiency, indicating that RTC promotes lower body weight in these models through effects on energy expenditure. Interestingly, both semaglutide and RTC treatment led to increased relative mass of the cecum, which may drive enhanced anaerobic resting metabolism.

Together, our data demonstrate that treatment with RTC positively modulates anaerobic EE, possibly by enhancing fermentation of the gut microbial community, and may represent a novel therapeutic in the treatment of obesity. Further, combination therapy with low dose semaglutide and RTC may be an effective treatment for diabetes and obesity. These studies have expanded the foundation by which the fascinating direct connections between gut bacterial metabolism and resting anaerobic energy expenditure can be explored.
Matthew Andrew Hadiono  
Curriculum Vitae  
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Education

2019 – Present  
Ph.D. Candidate  
Medical College of Wisconsin, Department of Microbiology & Immunology  
Advisor: John R. Kirby, Ph.D.

2017 – 2019  
Medical Student (M1-M2)  
Medical College of Wisconsin, Medical Scientist Training Program

2012 – 2016  
Bachelor of Science in Biology  
Case Western Reserve University

Research Experience

2019 – Present  
Doctoral Student  
Medical College of Wisconsin, Department of Microbiology & Immunology  
Advisor: John R. Kirby, Ph.D.

2015-2017  
Research Technologist  
Case Western Reserve University, Case Comprehensive Cancer Center  
Advisors: Sanford Markowitz, M.D., Ph.D. and Won Jin Ho, M.D.

2012-2015  
Research Technologist  
Case Western Reserve University, School of Medicine - Department of Dermatology  
Advisor: Daniel L. Popkin, M.D., Ph.D.

National Presentations

2022  
Modulation of Gut Microbial Metabolism and Energy Expenditure by Xenobiotics and Bacterial Metabolites. Poster, MD-PhD National Student Conference.

2022  
Modulation of Gut Microbial Metabolism and Energy Expenditure by Xenobiotics and Bacterial Metabolites. Poster, Molecular Genetics of Bacteria and Phages Meeting

2019  
Specialized Bacterial Metabolite, Reutericyclin, Deflects Antipsychotic-Induced Weight Gain: Investigating Modes of Action. Poster, Keystone
Publications


